REMARKS

Applicants request reconsideration of the outstanding rejections in light of the present amendments and remarks. Claims 1-57, 59-70, and 72 were canceled previously, without prejudice to the subject matter contained therein. Claims 58, 71, and 73-77 are pending. The pending claims have been amended, new claims 78-83 have been introduced herein. Support for the amendments and new claims may be found throughout the specification, for example at page 61, Examples 9 and 10, Tables 4-8, Figures 5, 7a, and 8a. No new matter is introduced by these amendments and entry is requested respectfully.

In particular, claim 58 has been amended to read:

> 58. A single assay device for distinguishing a leukemia of T-cell, B-cell, or myeloid lineage in a subject, said device comprising
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> a solid support selected from the group consisting of glass, cellulose, ceramic material, nitrocellulose, polyacrylamide, nylon, polystyrene, polystyrene derivatives, polyvinylidene difluoride, methacrylate, methacrylate derivatives, polyvinyl chloride, and polypropylene; and
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> an array of immunoglobulin molecules or antigen-binding fragments thereof immobilized in discrete regions on the solid support, wherein the immunoglobulin molecules or antigen-binding fragments thereof are specific for single distinct cell surface marker antigens comprising at least CD3, CD4, CD8, CD14, CD19, and CD56 on a leukocyte such that specific binding of the immunoglobulin molecule or antigen-binding fragment thereof of each discrete region to its respective distinct leukocyte cell surface marker antigen provides a pattern of cell binding on the array of discrete regions, each being specific for a single cell surface marker presented only once in the array, of the different leukocyte cell surface marker antigens comprising at least CD3, CD4, CD8, CD14, CD19 and CD56, that distinguishes leukemias of T-cell, B-cell, or myeloid lineage.

Rejections under 35 U.S.C. § 112

On page 2 of the Office Action, the Examiner rejects claims 58, 71, and 73-77 under 35 U.S.C. § 112, second paragraph "as being indefinite." Specifically, the Examiner asserts that the

recited phrase "derivatised solid support" lacks clarity. The claims have been amended to delete the term "derivatised." Hence, the rejection may now be withdrawn.

Rejections under 35 U.S.C. § 103

On page 3 of the Office Action, the Examiner rejects claims 58, 71, and 73-76 under 35 U.S.C. § 103 "as being unpatentable over the abstract of Gruber et al (Journal of Immunological Methods, 1993, Vol. 163, pp. 173-179) in view of Wysocki et al., (PNAS, 1978, Vol. 75, pp. 2844-2848) and Delmarche et al (Science, 1977, Vol. 276, pp. 779-781)." Applicants respectfully traverse the rejection.

The present invention provides for a single assay device for distinguishing a leukemia of T-cell, B-cell, or myeloid lineage in a subject, comprising a solid support selected from the group consisting of glass, cellulose, ceramic material, nitrocellulose, polyacrylamide, nylon, polystyrene, polystyrene derivatives, polyvinylidene difluoride, methacrylate, methacrylate derivatives, polyvinyl chloride, and polypropylene; and an array of immunoglobulin molecules or antigen-binding fragments thereof immobilized in discrete regions on the solid support, wherein the immunoglobulin molecules or antigen-binding fragments thereof are specific for single distinct cell surface marker antigens comprising at least CD3, CD4, CD8, CD14, CD19, and CD56 on a leukocyte, such that specific binding of the immunoglobulin molecule or antigen-binding fragment thereof of each discrete region to its respective distinct leukocyte cell surface marker antigen provides a pattern of cell binding on the array of discrete regions, each being specific for a single cell surface marker presented only once in the array, of the different leukocyte cell surface marker antigens comprising at least CD3, CD4, CD8, CD14, CD19 and CD56, that distinguishes leukemias of T-cell, B-cell, or myeloid lineage.

In use, the claimed device provides a visual pattern that provides a diagnosis in a single, rapid test, assisting clinicians to achieve a better understanding of their patient's condition and thus provide better treatment. Since the filing of the present patent application, this assay device has been applied to the analysis of over 700 patients and has proved over 90% accurate when compared to traditional techniques. Applicant's award-winning technology has been also been commercialized in Australia. It is without doubt a useful and life-saving invention.

The Examiner is aware of copending application Ser. No. 09/888,959, which application has been allowed. On page 3 of the Notice of Allowance mailed May 7, 2009, the Examiner stated as the reason for allowance:

> It is noted that the limitation "wherein each immunoglobulin region specific for said single surface marker is present only once in the array" is supported by originally filed figures 7a and 8a.

The pending claims presented herein also recite the limitation that "each [immunoglobulin or antigen binding fragment thereof] being specific for a single cell surface marker presented ***only once*** in the array."

Returning to the Office Action, the Examiner relies on the Gruber abstract which reads:

> New fluorescent monoclonal antibody-dye conjugates permit three-color immunofluorescence analysis of leukocytes in whole blood using a single laser flow cytometer. The fluorochrome used in this study is a tandem conjugate of phycoerythrin (PE) and Cyan-5, which is excitable at 488 nm with a maximum in the emission spectrum at > 650 nm and it can be used together with PE and fluorescein isothiocyanate (FITC). The directly labelled monoclonal antibodies are incubated with unseparated anticoagulated blood and subsequently erythrocytes are lysed by a standardized automated procedure. The resulting leukocyte suspension can then be analyzed for three different surface markers in an individual sample of 100 microliters blood. When compared simultaneously with single-color analysis triple-color immunofluorescence yielded identical quantitative and qualitative results on various lymphocyte subpopulations. The efficacy of this method was evaluated by analyzing leukocytes of 42 healthy donors for the following markers: CD3, CD4, CD8, CD14, CD16, CD19, CD25, CD38, CD45RO, CD45RA, CD56, CD57, TCR-gamma/delta and HLA-DR. Of special interest was the finding that CD45RA and CD45RO are differently expressed in CD4 and CD8 cells. The reliability and convenience of this three-color analysis will make it possible to do more sophisticated examinations of subpopulations and their relevance in the monitoring of autoimmune diseases, immunodeficiency syndromes including AIDS and malignant disorders such as leukemias.

The Examiner asserts that Gruber supports an obviousness rejection because it "teaches the detection of the cell surface markers of CD3, CD4, CD8, CD14, CD19 and CD56" Gruber refers to an assay using three-color flow cytometry to identify subsets of leukocytes: this technique is completely different from antibody microarrays. Flow cytometry utilizes fluid phase binding of antibodies to a cell surface, which is governed by mass action kinetics. The fundamental mechanism

of action utilized by the present invention operates by physiologically based cell adhesion and rate kinetics to a solid surface and is thus completely different to liquid phase cell interactions. Importantly, flow cytometry does not obtain the result in a ***single*** assay device, but instead requires assembly of assays three-at-a-time, and hence multiple samples would be required to achieve identification of subsets of leukocytes as in the claimed invention, assuming *arguendo* that would be possible at all under Gruber.

Indeed, comparisons between flow cytometry and the single solid support array of antibodies according to the present invention were made and can be found on pages 64-65 and Table 8 of the specification. These results show the superiority of the present invention over flow cytometry (and other prior art tests). The Examiner's reliance on prior art relating to flow cytometry has not been substantiated or justified in raising obvious rejections of the present invention.

Further regarding claim 58, Gruber does not suggest, teach or disclose any subset or combination of the CD markers listed in the abstract for diagnosis of T cell, B cell, or myeloid lineage in a subject as claimed by the present application. More specifically, there is no hint in Gruber that the claimed CD3, CD4, CD8, CD14, CD19 and CD56, as opposed to any other subset or combination of the fourteen markers listed the Gruber abstract, provides for the diagnosis of T-cell, B-cell, or myeloid lineage leukemia. Indeed, there are ***at least eighty-four combinations*** of panels of six markers that could be assembled from Gruber, including many that contain ***none*** of the claimed markers. Moreover, as mentioned above, the method of Gruber allows for the testing of only three markers at a time: "The resulting leukocyte suspension can then be analyzed for three different surface markers in an individual sample of 100 microliters blood." This greatly increases the number of possible combinations of assays that might be created to overlap with the claimed panel, with no suggestion as to which three markers would be more relevant than any other three for the diagnosis of leukemia.

The combination of Gruber, Wysocki, and Delmarche must suggest that this panel - CD3, CD4, CD8, CD14, CD19, and CD56 on the single array - can be used to distinguish leukemia of T-cell, B-cell, or myeloid lineage in the subject in need of such diagnosis - in order to support an obviousness rejection. Clearly, Gruber does not.

On page 4 of the Office Action, the Examiner asserts that Wysocki teaches that "lymphocytes from a heterogeneous population can bind to a solid support coated with an antibody specific for a cell surface antigen."

Wysocki refers to cell-capture by a single immobilized antibody ("panning for lymphocytes"), and there is no extensive dot pattern for the identification of subsets of leukocytes on a single array. Wysocki employed this method to ***fractionate*** and ***separate*** T and B lymphocytes (Abstract), and does not touch on the characterization of these cells as a pattern of cell binding in relation to the diagnosis of a T-cell, B-cell, or myeloid leukemia.

Wysocki does not suggest, teach, or disclose a complex cell surface phenotype for the identification of subsets of leukocytes. As such, Wysocki does not suggest, teach, or disclose the single device for distinguishing a leukemia of T-cell, B-cell, or myeloid lineage in a human subject as presently claimed. The microarrays of immobilized CD antibodies that are used to capture leukocytes expressing the complementary surface molecules (CD antigens) in Wysocki does not suggest, teach, or disclose the generation of extensive pattern of cell binding that provides the disease signatures of the claimed device.

Also on page 4 of the Office Action, the Examiner cites Delmarche for the teaching of "a method of applying different immunoglobulins in a pattern on a derivatised solid support with high resolution and glass ..." Delmarche refers to schemes for using one or two different IgGs (mouse and chicken) in a ***micro-fluidic network*** and a relatively crude system for applying patterns of antibodies to a surface. Delmarche presents work related to immunoglobulin-immunoglobulin binding. Delmarche does not suggest, teach or disclose extensive profiles of cell surface molecules or of mixed populations of proteins as a diagnostic tool. Any patterns mentioned in Delmarche have no bearing on the diagnosis of leukemias. Moreover, as with Gruber and Wysocki, Delmarche does not suggest using a specific panel of six markers (CD3, CD4, CD8, CD14, CD19, and CD56), each present once on an array, for the characterization of cells in relation to the diagnosis of a T-cell, B-cell, or myeloid leukemia.

In re O'Farrell, is instructive on the present rejection:

> The admonition that "obvious to try" is not the standard has been directed mainly at two kinds of error. In some cases, ***what would have been "obvious to try" would have been to vary all parameters or to try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many choices were likely to be successful.*** … In others what was "obvious to try" was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave ***only general guidance*** as to the ***particular form*** of the claimed invention or how to achieve it. *In re O'Farrell*, 7 USPQ2d 1673 (Fed. Cir. 1988) (emphasis added).

Gruber's list of markers provides numerous possible choices of markers, with no indication of which parameters are critical or which of the myriad of choices are likely to provide for panel of six markers (CD3, CD4, CD8, CD14, CD19, and CD56) for the characterization of cells in relation to the diagnosis of a T-cell, B-cell or myeloid leukemia. The technologies of Wysocki and Delmarche provide, at best, only general guidance to the array of the present invention. By contrast, the present invention delivers a complex multiplexed phenotype for distinguishing a leukemia of T-cell, B-cell, or myeloid lineage in a subject for which the combination of the cited art does not teach or suggest to the skilled person any more than do the individual documents. The presently claimed invention is inventive over any combination of the cited prior art. Hence, because this § 103 rejection is inadequately supported by the cited references, Applicants respectfully request that it be withdrawn.

Moreover, the Court has instructed that objective evidence relevant to the issue of obviousness, i.e., secondary factors, ***must*** be evaluated by Office personnel. *Graham v. John Deere Co.*, 383 U.S. 1 (1966). Such evidence may include evidence of commercial success, long-felt but unsolved needs, failure of others, and unexpected results. Applicants have provided the Examiner with a MEDSAIC press release, which reports that Applicants' licensee received the 2005 "BioFirst Commercialisation Award" for outstanding achievement in technology for its leukemia and lymphoma diagnostic. In addition to the recognition of commercial development and success in Australia, MEDSAIC was deemed most likely to achieve international success with its technology. This award evidences the recognition of others and commercial success of the claimed invention.

Applicants also provided the Examiner with a pier-reviewed article validating the Applicants application of the instant technology: Belov et al., "Analysis of Human Leukemias and Lymphomas Using Extensive Immunophenotypes from an Antibody Microarray," 135 British Journal of Haematology, 134-97 (2006). This paper clearly evidences the improvement over any of the techniques addressed in the art cited by the Examiner.

In summary, comparing all of the cited references, in combination, to the claimed invention, it is clear that claimed invention reflects an advancement and "real innovation." *KSR Int'l. Co v. Teleflex Inc.*, 127 S.Ct. 1727 (2007). Hence, Applicants request that the § 103 rejections be withdrawn.

On page 6 of the Office Action, the Examiner rejects claim77 "as being unpatentable over the abstract of Gruber et al … in view of Wysocki et al. … and Delmarche et al … and further in view of Dano et al. (US 5,519,120)." Applicants respectfully traverse the rejection.

The Examiner asserts that Dano describes "a nitrocellulose glass slide and using various antibodies, including monoclonal and polyclonal antibodies as well as using complexing agents such as protein G to form a complex with immunoglobulins and link to a solid support (col. 17, second and third paragraphs; and col. 19, fourth to seventh paragraphs; col. 83, sixth paragraph." The cited paragraphs read:

> For purposes not requiring a high assay specificity, the antibody may be a polyclonal antibody. Polyclonal antibodies may be obtained, e.g. as described …. More specifically, when polyclonal antibodies are to be obtained, the u-PAR compound preparation is, preferably after addition of a suitable adjuvant, such as Freund's incomplete or complete adjuvant, injected into an animal. When the immunogens are human u-PAR compounds, the animals may be rabbits. The animals are bled regularly, for instance at weekly intervals, and the blood obtained is separated into an antibody containing serum fraction, and optionally said fraction is subjected to further conventional procedures for antibody purification, and/or procedures involving use of purified u-PAR compounds.
>
> In another preferred embodiment, monoclonal antibodies are obtained. The monoclonal antibody may be raised against or directed substantially against an essential component of u-PAR compounds, i.e. an epitope. The monoclonal antibody may be produced by conventional techniques … e.g. by use of a hybridoma cell line, or by clones or subclones thereof or by cells carrying genetic information from the hybridoma cell line coding for said monoclonal antibody. The monoclonal antibody may be produced by fusing cells producing the monoclonal antibody with cells of a suitable cell line, and selecting and cloning the resulting hybridoma cells producing said monoclonal antibody. Alternatively, the monoclonal antibody may be produced by immortalizing an unfused cell line producing said monoclonal antibody, subsequently growing the cells in a suitable medium to produce said antibody, and harvesting the monoclonal antibody from the growth medium. (Col. 17, internal citations omitted)

> In an embodiment of the invention an antibody of the invention may be coupled to a bridging compound coupled to a solid support. The bridging compound, which is designed to link the solid support and the antibody may be hydrazide, Protein A, glutaraldehyde, carbodiimide, or lysine.
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> The solid support employed is e.g. a polymer or it may be a matrix coated with a polymer. The matrix may be of any suitable solid material, e.g. glass, paper or plastic. The polymer may be a plastic, cellulose such as specially treated paper. nitrocellulose paper or cyanogenbromide-activated paper. Examples of suitable plastics are latex, a polystyrene, polyvinylchloride, polyurethane, polyacrylamide, polyvinylacetate and any suitable copolymer thereof. Examples of silicone polymers include siloxane.

The solid support may be in the form of a tray, a plate such as a mitrotiter plate, e.g. a thin layer or, preferably, strip, film, threads, solid particles such as beads, including Protein A-coated bacteria, or paper. (Col. 19)

The next paragraph, not cited by the Examiner, gives the context for such embodiment:

The antibody of the invention may be used in an assay for the identification and/or quantification of at least a form and/or a part of said ***polypeptide*** present in a sample. The identification and/or quantification performed by the use according to the present invention may be any identification and/or quantification involving u-PAR compounds or a form of u-PAR compounds. Thus, both a qualitative and a quantitative determination of u-PAR compounds may be obtained according to the use of the present invention. The identification and/or quantification may be performed for both a scientific, a clinical and an industrial purpose. As will be further described below, it is especially important in clinical routine to identify or quantify u-PAR compounds. (Col. 19)

Cells in culture were plated on glass slides and allowed to grow for two days before they were fixed with 0.5% (vol/vol) glutaraldehyde in PBS for 5 minutes followed by 3 times wash with PBS and overnight incubation at 37°C in X-gal staining solution (1 mg of X-gal/ml; 35 mM potassium ferricyanide; 2 mM $MgCl_2$ in PBS). The sections were counterstained with Kernechtrot. (Col. 83)

The Examiner, on page 7 of the Office Ation, cites the Dano Field of the Invention:

The present invention relates to important further developments of certain aspects of the invention disclosed in International Patent Application No. PCT/DK90/00090, and U.S. patent application Ser. Nos. 334,613 and 374,854, the developments of the present invention relating, in particular, to special types of antibodies, especially monoclonal antibodies, and the use of these special types of antibodies, in particular for detecting and quantitating u-PAR, for therapeutic use, and for drug screening.

None of the cited paragraphs relate at all to leukemia, or the diagnosis of a leukemia type by leukocyte binding to an array. In fact, none of the 84 columns of Dano mention to the diagnosis of leukemia by leukocyte binding to an array in a pattern. Instead, Dano relates to the characterization of u-PAR peptides. Certainly Dano never suggests using a specific panel of six markers (CD3, CD4, CD8, CD14, CD19, and CD56), each present once on an array that provides for a pattern of cell binding in relation to the diagnosis of a T-cell, B-cell, or myeloid leukemia. Indeed, none of the cited references refer to an array that is in any way analogous to the array of the instant claimed device.

Moreover, the particular elements of the cited references simply do not provide the instant CD antibody microarray. The Examiner should recognize the difference between piecemeal acquisition of a limited surface expression profile using multiple analyses by flow cytometry (Gruber), and the acquisition of a far more extensive profile in one assay device that uses distinct leukocyte cell surface marker antigens to provide a pattern of binding on an array of discrete regions. Although Dano refers to nitrocellulose as a support for antibodies, there is no array and live cells are not capture, as compared to the claimed invention. Cell capture by immobilized antibodies was described by Wysocki as "panning for lymphocytes." The claimed invention, however, provides a single assay device that can generate extensive "patterns of recognition" or "disease signatures" from a microarray of immobilized CD antibodies that are used to distinguish leukemias of T-cell, B-cell, or myeloid lineage. Hence, because this § 103 rejection is inadequately supported by the cited references, and because the Applicants have provided the requisite secondary considerations in support of the instant claims, Applicants respectfully request that this rejection be withdrawn.

CONCLUSION

Applicants respectfully request reconsideration of this application and allowance of the pending claims in view of the above remarks.

Except for issue fees payable under 37 C.F.R. §1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account No. 19-2380. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. §1.136(a)(3).

Respectfully submitted,

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